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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/695,578	10/27/2003	Scott A. Waldman	08321-0157 CT1	5382

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EXAMINER	
AEDER, SEAN E	
ART UNIT	**PAPER NUMBER**
1642	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

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Office Action Summary	Application No.	Applicant(s)	
	10/695,578	WALDMAN, SCOTT A.	
	Examiner	Art Unit	
	Sean E. Aeder, Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 February 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *24-46* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *24-46* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

The Amendments and Remarks filed 2/27/07 in response to the Office Action of 9/13/06 are acknowledged and have been entered.

Claims 24-46 are pending.

Claims 24-29, 36-39 have been amended by Applicant.

Claims 24-46 are currently under examination.

The following Office Action contains NEW GROUNDS of rejections necessitated by amendments.

Rejections Withdrawn

Due to amendments to the claims, which changed the scope of the invention, the rejections set forth in the Office Action of 9/13/06 are withdrawn.

New Rejections Necessitated by Amendments

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 24-46 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 24-29, 36-39, and dependent claims 30-35 and 40-46 are rejected as vague and indefinite because claims 24-29 and 36-39 recite the term "guanylyl cyclase C" as the sole means of identifying the polynucleotides of the claimed method. The use of laboratory designations only to identify a particular molecule renders the claims indefinite because different laboratories may use the same laboratory designations to define completely distinct molecules. Amending the claims to specifically and uniquely identify human guanylyl cyclase C by SEQ ID NO can obviate the rejection.

In the Response of 2/27/07, Applicant states that the term "ST receptor" and "guanylyl cyclase C" are used interchangeably in the art. Applicant further states that those of skill in the art would readily know the metes and bounds of the claims based upon the reference to guanylyl cyclase C, which Applicant states is a well known protein having specific structure and function.

The arguments found in the Response of 2/27/07 have been carefully considered, but are not deemed persuasive. In regards to the argument that the term "ST receptor" and "guanylyl cyclase C" are used interchangeably in the art, the teachings of Almenoff et al (journal of Biological Chemistry, 6/17/94, 269(24):16610-16617) demonstrate that colorectal cancer cells have ST receptors other than guanylyl cyclase C (see page 16611, in particular). Further, the instant specification discloses the terms "ST receptor" and "guanylin cyclase C" are interchangeable and are broadly meant to refer to receptors found on colorectal cancer cells which bind to ST (see page 7). Therefore, "guanylyl cyclase C" must be an ST receptor species and is not synonymous with the genus encompassed by "ST receptor".

In regards to the argument that those of skill in the art would readily know the metes and bounds of the claims based upon the reference to guanylyl cyclase C, the Response of 2/27/07 in light of the teachings of Almenoff et al demonstrates that the metes and bounds of the claims are not clear based upon the reference to guanylyl cyclase C. The Response indicates "ST receptor" and "guanylyl cyclase C" are synonymous; however, the teaching of Almenoff et al clearly demonstrate that a protein referred to as guanylyl cyclase C is a species of ST receptor.

Claims 26, 27, 36, and 37 are rejected for reciting "the extracellular domain of the human guanylyl cyclase C protein". As stated above, it is unclear what is meant by "guanylyl cyclase C". Therefore, it is unclear what part of guanylyl cyclase C would be the extracellular domain of human guanylyl cyclase C. Further, it is noted that the specification does not disclose which region of human guanylyl cyclase C is an extracellular domain. Given the above reasons, the metes and bounds of the claims cannot be determined.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 24-46 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter which was not described in the specification in such a way as to reasonably convey to

one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. In the instant case, the claims are inclusive of: (1) a genus of polynucleotides encoding human guanylyl cyclase C protein and (2) a genus of polynucleotides encoding the extracellular domain of human guanylyl cyclase C. The specification does not disclose the term "guanylyl cyclase C". Further, the specification does not disclose "the extracellular domain of human guanylyl cyclase C".

The prior at does not teach the genera discussed above, which, as indicated by the instant specification and the Reply of 2/27/07, encompasses polynucleotides encoding every receptor found on colorectal cells that binds ST and polynucleotides encoding the extracellular domains of said receptors (see Reply of 2/27/07 and lines 17-25 on page 7 of the Specification).

A description of a genus may be achieved by means of a recitation of a representative number of species falling within the scope of the genus or by describing structural features common to that genus that "constitute a substantial portion of the genus." See University of California v. Eli Lilly and Co., 119 F.3d 1559, 1568, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997): "A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNA, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus."

The court has since clarified that this standard applies to compounds other than cDNAs. See University of Rochester v. G.D. Searle & Co., Inc., F.3d, 2004 WL 260813,

at *9 (Fed.Cir.Feb. 13, 2004). The instant specification fails to provide sufficient descriptive information, such as definitive structural or functional features that are common to the genus. That is, the specification provides neither a representative number of sequences that encompass the genera nor does it provide a description of structural features that are common to said genera. Since the disclosure fails to describe common attributes or characteristics that identify members of the genera, and because the genera are highly variant, the disclosure of a human ST receptor SEQ ID NO is insufficient to describe the genera. Thus, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe and enable the genus as broadly claimed.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genera, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolation. The compound

itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

In the Response of 2/27/07, Applicant states the claims have been amended to refer to "guanylyl cyclase C" instead of "ST receptor". Applicant further states that those of skill in the art would recognize that the two terms are interchangeable and guanylyl cyclase C is the more common term for the same protein as ST receptor and has a specific structure and function.

The arguments found in the Response of 2/27/07 have been carefully considered, but are not deemed persuasive. In regards to the argument that the term "ST receptor" and "guanylyl cyclase C" are used interchangeably in the art and refer to the same protein with known structure and function, the teachings of Almenoff et al (journal of Biological Chemistry, 6/17/94, 269(24):16610-16617) demonstrate that colorectal cancer cells have ST receptors other than guanylyl cyclase C (see page 16611, in particular). Further, the instant specification discloses the terms "ST receptor" and "guanylin cyclase C" are interchangeable and are broadly meant to refer to receptors found on colorectal cancer cells which bind to ST (see page 7). Therefore,

"guanylyl cyclase C" must be an ST receptor species and is not synonymous with the genus of "ST receptor". The specification does not provide a written description of polynucleotides encoding "human guanylyl cyclase C" or polynucleotides encoding the extracellular domain of "human guanylyl cyclase C".

Claims 24-46 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether undue experimentation is required, are summarized in *In re* Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and the quantity of experimentation needed to make or use the invention based on the content of the disclosure. See also *Ex parte* Forman, 230 USPQ 546 (BPAI 1986).

The claims are broadly drawn to a method of treating an individual who has metastasized colorectal cancer or an individual who is susceptible to metastasized colorectal cancer with an immunotherapeutic vaccine comprising a nucleic acid molecule encoding at least one epitope of human guanylyl cyclase C.

The specification prophetically describes methods of treating an individual who has metastasized colorectal cancer or an individual who is susceptible to metastasized colorectal cancer with a vaccine comprising a nucleic acid molecule encoding at least one epitope of human ST receptor protein (page 11-12, in particular). However, the specification lacks working examples using a vaccine comprising a nucleic acid molecule encoding at least one epitope of human guanylyl cyclase C or human ST receptor protein to treat any individual.

Further, the specification does not provide a written description of methods involving polynucleotides encoding "human guanylyl cyclase C" or polynucleotides encoding the extracellular domain of "human guanylyl cyclase C". Therefore, the specification does not provide guidance for the claimed method, which requires use of polynucleotides encoding "human guanylyl cyclase C" or polynucleotides encoding the extracellular domain of "human guanylyl cyclase C".

Further, therapeutic treatments, in general, are unpredictable. With regards to tumor immunotherapy, the goal of tumor vaccination is the induction of tumor immunity to prevent tumor recurrence and to eliminate residual disease. However, gene therapy against tumors is highly unpredictable as underscored by Crystal, R.G. (Science, Vol. 270, October 1995, pages 404-410) who teaches that in tumor vaccine studies intended

to evoke a tumor-directed immune response, there is no convicining evidence (other than anecdotal case reports) that tumors actually regress, despite the promising observations in experimental animals. In other words, humans are not simply large mice (page 409, 1st column). More recently, Tait *et al.* (Clin.Canc.Res., Vol. 5, July 1999, pages 1708-1714) revealed just how unpredictable gene therapy was in the clinical setting. The authors' prior phase I trial of 12 patients with extensive ovarian cancer treated with a retroviral vector expressing the BRCA1 splice variant (LXSN-BRCA1sv) demonsrated vector stability, minimal immune response, gene transfer and expression, and some tumor reduction in the patients (page 1708, 2nd column, 2nd paragraph). In contrast, the Phase II trial inititiated in pateints with stage III and IV grade ovarian cancer, showed a high preponderance for vector instability (vector was degraded rapidly), a rapid immunological response invoking neutralizing antibodies to the retroviral vector, and no clinical response to the therapy. Although the difference in response to the therapy may be attributed to differences in immunocompetence between the phase I and II patients (page 1712, 2nd column), the end result seems to indicate that further experimentation is necessary prior to the successful application of DNA vaccines, especially with the regards to cancer therapy. Further, therapeutic cancer treatments, in general, are unpredictable, as underscored by Gura (Science, 1997, 278:1041-1042.) who discusses the potential shortcoming of potential anti-cancer agents including extrapolating from in-vitro to in-vivo protocols, the problems of drug testing in knockout mice, and problems associated with cologenic assays. Indeed, since formal screening began in 1955, thousands of drugs have shown activity in either

cell or animal models, but only 39 that are used exclusively for chemotherapy, as opposed to supportive care, have won approval from the FDA (page 1041 first column, in particular) wherein the fundamental problem in drug discovery for cancer is that the model systems are not predictive.

Further, those of ordinary skill in the art recognize that treatment in vivo is not predictive. The instant situation is analogous to that of *In re* Brana (34 U.S.P.Q. 2d 1436, 1440 (Fed. Cir. 1995)). A review of *In re Brana* reveals an application that claimed a chemical compound for treating a cancer, wherein the chemical compound was structurally similar to known compounds that have known in vivo use to treat tumors, and more importantly, Applicant provided in vivo data that the claimed compound could treat tumors in mice, hence it was ruled that the claimed compound was enabled for treating tumors. In the instant application, the claim is not drawn to a vaccine comprising a nucleic acid molecule encoding at least one epitope of human guanylyl cyclase C receptor protein which has known in vivo ability to give rise to a therapeutic effect. Further, the instant specification provides no in vivo data, particularly demonstrating that the claimed vaccine would predictably give rise to a therapeutic effect in vivo. In view of *In re Brana*, Examiner asserts that successful use of in vivo mouse models of colon cancer enables compositions for specific therapeutic effects in humans and does not require human clinical testing; however, the instant application is claiming a vaccine that provides a therapeutic effect without providing any in vivo data, hence the claimed invention is not enabled. All of this underscores the criticality of providing workable examples which are not disclosed in the specification, particularly in

an unpredictable art, such as vaccine treatment.

In view of the teachings above and the lack of predictability, guidance, workable examples and or exemplification in the specification, it would require undue experimentation by one of skill in the art to make the invention.

In the Response of 2/27/07, Applicant submitted an un-signed declaration by Scott Waldman. Applicant states that the declaration states that administration of protein comprising guanylyl cyclase C (GCC) extracellular domain induced robust antigen-specific T cell responses. Applicant further states that the declaration states that administration of an adenovirus vector construct expressing the extracellular domain of GCC was effective in vivo in tumor challenge models.

The arguments found in the Response of 2/27/07 have been carefully considered, but are not deemed persuasive. In regards to the argument that the declaration states that administration of protein comprising guanylyl cyclase C (GCC) extracellular domain induced robust antigen-specific T cell responses, the claims are drawn to providing prophylactic and/or therapeutic effects to individuals comprising administering polynucleotides. Further, one of skill in the art would recognize that a robust antigen-specific T cell response does not predictably result in a prophylactic and therapeutic effects to individuals who have or who are susceptible to metastatic colorectal cancer. In regards to the argument that administration of an adenovirus vector construct expressing the extracellular domain of GCC was effective in vivo in tumor challenge models, the in vivo model presented in the declaration is not representative of colorectal cancer metastasis in vivo. In fact, the colon cancer cells

used in the in vivo model were stably transfected with GCC. Therefore, the effects of the adenovirus vector construct expressing the extracellular domain of GCC were not shown to target colorectal cancer cells. Rather, the adenovirus was shown to target cells *artificially expressing a target*. Therefore, it remains unpredictable whether polynucleotides encoding GCC would provide therapeutic and prophylactic effects in an in vivo environment where cells are not *artificially overexpressing* GCC. Further, Applicant is again reminded that the specification does not provide a written description of methods involving polynucleotides encoding "human guanylyl cyclase C" or polynucleotides encoding the extracellular domain of "human guanylyl cyclase C". Therefore, the specification does not provide guidance for the claimed method, which requires use of polynucleotides encoding "human guanylyl cyclase C" or polynucleotides encoding the extracellular domain of "human guanylyl cyclase C".

New Matter

Claims 24-46 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a **NEW MATTER** rejection.

Claims 24-46 recite methods comprising using polynucleotides encoding human guanylyl cyclase C and method using polynucleotides encoding the extracellular domain of human guanylyl cyclase C. Descriptions of polynucleotides encoding human guanylyl

cyclase C and method using polynucleotides encoding the extracellular domain of human guanylyl cyclase C are not found in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the invention was filed, had possession of the claimed invention.

In the Response of 2/27/07, Applicant states that the term "ST receptor" and "guanylyl cyclase C" are used interchangeably in the art. Applicant further states that those of skill in the art would readily know the metes and bounds of the claims based upon the reference to guanylyl cyclase C, which Applicant states is a well known protein having specific structure and function.

The arguments found in the Response of 2/27/07 have been carefully considered, but are not deemed persuasive. In regards to the argument that the term "ST receptor" and "guanylyl cyclase C" are used interchangeably in the art, the teachings of Almenoff et al (journal of Biological Chemistry, 6/17/94, 269(24):16610-16617) demonstrate that colorectal cancer cells have ST receptors other than guanylyl cyclase C (see page 16611, in particular). Further, the instant specification discloses the terms "ST receptor" and "guanylin cyclase C" are interchangeable and are broadly meant to refer to receptors found on colorectal cancer cells which bind to ST (see page 7). Therefore, "guanylyl cyclase C" must be an ST receptor species and is not synonymous with the genus of "ST receptor". Therefore, polynucleotides encoding human guanylyl cyclase C and polynucleotides encoding the extracellular domain of human guanylyl cyclase C are species that are not disclosed specification.

Summary

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a). A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sean E. Aeder, Ph.D. whose telephone number is 571-272-8787. The examiner can normally be reached on M-F: 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shanon Foley can be reached on 571-272-0898. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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